PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 311/22, 335/06, 215/22, 311/30, 311/24, A01N 43/16

A1

(11) International Publication Number: **WO 98/27080**

(43) International Publication Date: 25 June 1998 (25.06.98)

(21) International Application Number: PCT/GB97/03368

(22) International Filing Date: 18 December 1997 (18.12.97)

(30) Priority Data:

9626322.3	19 December 1996 (19.12.96)	GB
9707270.6	10 April 1997 (10.04.97)	GB
9707271.4	10 April 1997 (10.04.97)	GB
9707272.2	10 April 1997 (10.04.97)	GB

(81) Designated States: AU, BR, CA, CN, HU, IL, JP, KR, MX, PL, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(71) Applicant *(for all designated States except US)*: AGREVO UK LIMITED [GB/GB]; Hauxton, Cambridge CB2 5HU (GB).

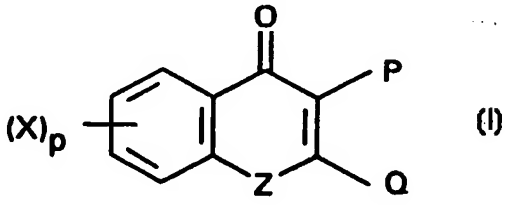
(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MACRITCHIE, Jacqueline, Anne [GB/GB]; Chesterford Park, Saffron Walden, Essex CB10 1XL (GB). O'MAHONY, Mary, Josephine [IE/GB]; Chesterford Park, Saffron Walden, Essex CB10 1XL (GB). LINDELL, Stephen, David [GB/DE]; c/o Hoechst Aktiengesellschaft, D–65926 Frankfurt am Main (DE).

(74) Agent: WALDMAN, Ralph, David; AgrEvo UK Limited, Patent Dept., Chesterford Park, Saffron Walden, Essex CB10 1XL (GB).

(54) Title: CHROMONES USEFUL AS FUNGICIDES

(57) Abstract



(I)

Compounds of formula (I) in which Z is O, $S(O)_n$ or NR, and a) P is WR^2; and Q is R^1 or W^2R^{2a} or b) P is R^a and Q is R^b; and when Z is $S(O)_n$ or NR, and Q is W^2R^{2a}; P can be R^1; W and W^2, which may be the same or different, are O, $S(O)_n$, $N(R^3)$, $N(R^3)N(R^4)$, $N(R^3)O$ or $ON(R^3)$; R^1 is hydrogen, or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, phenyl or heterocyclyl group; R, R^2, R^{2a}, R^{2b}, R^3 and R^4, which may be the same or different, have the same meaning as R^1, or are acyl, or any two adjacent R groups together with the atoms to which they are attached form an optionally substituted ring which may contain other heteroatoms; R^a and R^b, which may be the same or different, have the same meaning as R^1 (heterocyclyl groups being carbon linked) or are cyano, nitro, $COOR^1$ or COR^1, each X, which may be the same as or different from any other X, is halogen, CN, NO_2, SF_5, $B(OH)_2$, trialkylsilyl or a group E, OE or SE where E is a group as defined hereinbefore for R^a or is optionally substituted amino; or two adjacent groups X together with the atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring; n is 0, 1 or 2; and p is 0 to 4 have fungicidal activity.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

CHROMONES USEFUL AS FUNGICIDES

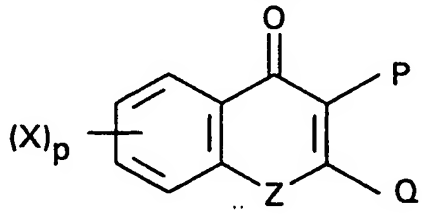
Field of the invention

This invention relates to chromones useful as fungicides.

Description of the invention

We have now found that certain chromones have particularly valuable fungicidal properties

In one aspect, the invention provides the use as fungicides of compounds of formula I



(I)

in which

Z is O, $S(O)_n$ or NR, and

a) P is WR^2; and Q is R^1 or W^2R^{2a} or

b) P is R^a and Q is R^b;

and when Z is $S(O)_n$ or NR, and Q is W^2R^{2a}; P can be R^1;

W and W^2, which may be the same or different, are O, $S(O)_n$, $N(R^3)$, $N(R^3)N(R^4)$, $N(R^3)O$ or $ON(R^3)$;

R^1 is hydrogen, or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, phenyl or heterocyclyl group;

R, R^2, R^{2a}, R^{2b}, R^3 and R^4, which may be the same or different, have the same meaning as R^1, or are acyl, or

any two adjacent R groups together with the atoms to which they are attached form an optionally substituted ring which may contain other hetero atoms;

R^a and R^b, which may be the same or different, have the same meaning as R^1 (heterocyclyl groups being carbon linked) or are cyano, nitro, $COOR^1$ or COR^1,

each X, which may be the same as or different from any other X, is halogen, CN, NO_2, SF_5, $B(OH)_2$, trialkylsilyl or a group E, OE or SE wher E is a group as

defined hereinbefore for R^a or is optionally substituted amino; or two adjacent groups X together with the atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

n is 0, 1 or 2; and

p is 0 to 4.

with the proviso that P and Q are not both hydrogen.

Many of the compounds are novel and the invention thus includes these novel compounds.

Any alkyl group present in the molecule is preferably of 1 to 10 carbon atoms, especially of 1 to 7 carbon atoms, and particularly of 1 to 5 carbon atoms, and may be straight or branched.

Any alkenyl or alkynyl group present in the molecule, may be straight or branched. and is preferably of 2 to 7 carbon atoms, for example allyl, vinyl or propargyl.

Any cycloalkyl, cycloalkenyl or cycloalkynyl group present in the molecule is preferably of 3 to 7 carbon atoms, especially cyclopropyl, cyclopentyl, or cyclohexyl.

Substituents, when present on any alkyl, alkenyl, alkynyl or cycloalkyl, cycloalkenyl or cycloalkynyl moiety may for example be halogen, cyano, trialkylsilyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkoxy, optionally substituted alkylthio, hydroxy, nitro, optionally substituted amino, acyl, acyloxy, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted phenylthio, optionally substituted phenoxy, optionally substituted heterocyclyloxy, optionally substituted heterocyclylthio or oxidised derivatives of thio-containing groups. Cycloalkyl , cycloalkenyl or cycloalkynyl groups may also be substituted by alkyl. alkenyl or alkynyl

The term heterocyclyl includes both heteroaryl groups as described below and non-aromatic heterocyclyl groups.

Heteroaryl groups are generally 5- or 6-membered rings containing up to 4 hetero atoms selected from nitrogen, oxygen and sulfur, optionally fused to a benzene ring.

Examples of heteroaryl groups are those derived from thiophene, furan, pyrrole, thiazole, oxazole, imidazole, isothiazole, isoxazole, pyrazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,4-triazole, 1,2,3-triazole, tetrazole, benzo[b]thiophene, benzo[b]furan, indole, benzo[c]thiophene, benzo[c]furan, isoindole, benzoxazole, benzothiazole, benzimidazole, benzisoxazole, benzisothiazole, indazole, benzothiadiazole, benzotriazole, dibenzofuran, dibenzothiophene, carbazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,3,5-triazine, 1,2,4-triazine, 1,2,4,5-tetrazine, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, 1,8-naphthyridine, 1,5-naphthyridine, 1,6-naphthyridine, 1,7-naphthyridine, phthalazine, pyridopyrimidine, purine or pteridine.

Non-aromatic heterocyclyl groups are generally 3, 5, 6 or 7-membered rings containing up to 3 hetero atoms from nitrogen, oxygen and sulfur, for example oxiranyl, thiiranyl, thiazolinyl, dioxolanyl, 1,3-benzoxazinyl, 1,3-benzothiazinyl, morpholino, pyrazolinyl, sulfolanyl, dihydroquinazolinyl, piperidinyl, phthalimido, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, indolinyl, 2-oxopyrrolidino, 2-oxobenzoxazolin-3-yl or tetrahydroazepinyl.

Substituents when present on any phenyl or heterocyclyl group may for example be halogen, CN, NO_2, SF_5, $B(OH)_2$, trialkylsilyl, acyl, O-acyl or a group E, OE or $S(O)_nE$, where E is as defined hereinbefore for R^3 or is acyl or optionally substituted amino; or two adjacent groups on the ring together with the atoms to which they are attached form a carbocyclic or heterocyclic ring, which may be similarly substituted.

The term acyl includes the residue of sulfur and phosphorus-containing acids as well as carboxylic acids. Examples of acyl groups are thus $-COR^5$, $-COOR^5$, $-CLNR^5R^6$, $-CON(R^5)OR^6$, $-COONR^5R^6$, $-CON(R^5)NR^6R^7$, $-COSR^5$, $-CSSR^5$, $-S(O)_qR^5$, $-S(O)_2OR^5$, $-S(O)_qNR^5R^6$, $-P(=L)(OR^5)(OR^6)$ or $-COOR^5$, where R^5, R^6 and R^7, which may be the same or different, are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted phenyl or optionally substituted heterocyclyl, or R^5 and R^6, or R^6 and R^7, together with the atom(s) to which they are attached can form a ring, q is 1 or 2 and L is O or S.

Amino groups may be substituted for example by one or two optionally substituted alkyl or acyl groups, or two substituents can form a ring, preferably a 5- to 7-membered ring, which may be substituted and may contain other hetero atoms, for example morpholine.

The invention also includes the compounds falling within formula I disclosed in the Examples.

The compounds of the invention have activity as fungicides, especially against fungal diseases of plants, e.g. mildews and particularly cereal powdery mildew (*Erysiphe graminis*), vine powdery mildew (*Uncinula necator*), vine downy mildew (*Plasmopara viticola*), rice blast (*Pyricularia oryzae*), cereal eyespot (*Pseudocercosporella herpotrichoides*), rice sheath blight (*Pellicularia sasakii*), grey mould (*Botrytis cinerea*), damping off (*Rhizoctonia solani*), wheat brown rust (*Puccinia recondita*), late tomato or potato blight (*Phytophthora infestans*), apple scab (*Venturia inaequalis*), glume blotch (*Leptosphaeria nodorum*). Other fungi against which the compounds may be active include other powdery mildews, other rusts, and general pathogens of Deuteromycete, Ascomycete, Phycomycete and Basidiomycete origin.

The invention thus also provides a method of combating fungi at a locus infested or liable to be infested therewith, which comprises applying to the locus a compound of formula I.

The invention also provides an agricultural composition comprising a compound of formula I in admixture with an agriculturally acceptable diluent or carrier.

The composition of the invention may of course include more than one compound of the invention.

In addition the composition can comprise one or more additional active ingredients, for example compounds known to possess plant-growth regulant, herbicidal, fungicidal, insecticidal or acaricidal properties. Alternatively the compound of the invention can be used in sequence with the other active ingredient.

The diluent or carrier in the composition of the invention can be a solid or a liquid optionally in association with a surface-active agent, for example a dispersing agent, emulsifying agent or wetting agent. Suitable surface-active agents include anionic compounds such as a carboxylate, for example a metal carboxylate of a long chain fatty acid; an N-acylsarcosinate; mono- or di-esters of phosphoric acid with fatty alcohol ethoxylates or salts of such esters; fatty alcohol sulfates such as sodium dodecyl sulfate, sodium octadecyl sulfate or sodium cetyl sulfate; ethoxylated fatty alcohol sulfates; ethoxylated alkylphenol sulfates; lignin sulfonates; petroleum sulfonates; alkyl-aryl sulfonates such as alkyl-benzene sulfonates or lower alkylnaphthalene sulfonates, e.g. butyl-naphthalene sulfonate; salts of sulfonated naphthalene-formaldehyde condensates; salts of sulfonated phenol-formaldehyde condensates; or more complex sulfonates such as the amide sulfonates, e.g. the sulfonated condensation product of oleic acid and N-methyl taurine or the dialkyl sulfosuccinates, e.g. the sodium sulfonate of dioctyl succinate. Nonionic agents include condensation products of fatty acid esters, fatty alcohols, fatty acid amides or fatty-alkyl- or alkenyl-substituted phenols with ethylene oxide, fatty esters of polyhydric alcohol ethers, e.g. sorbitan fatty acid esters, condensation products of such esters with ethylene oxide, e.g. polyoxyethylene sorbitan fatty acid esters, block copolymers of ethylene oxide and propylene oxide, acetylenic glycols, such as 2,4,7,9-tetramethyl-5-decyne-4,7-diol, or ethoxylated acetylenic glycols.

Examples of a cationic surface-active agent include, for instance, an aliphatic mono-, di-, or polyamine as an acetate, naphthenate or oleate; an oxygen-containing amine such as an amine oxide or polyoxyethylene alkylamine; an amide-linked amine prepared by the condensation of a carboxylic acid with a di- or polyamine; or a quaternary ammonium salt.

The compositions of the invention can take any form known in the art for the formulation of agrochemicals, for example, a solution, a dispersion, an aqueous emulsion, a dusting powder, a seed dressing, a fumigant, a smoke, a dispersible powder, an emulsifiable concentrate or granules. Moreover it can be in a suitable form for direct application or as a concentrate or primary composition which requires dilution with a suitable quantity of water or other diluent before application.

An emulsifiable concentrate comprises a compound of the invention dissolved in a water-immiscible solvent which is formed into an emulsion with water in the presence of an emulsifying agent.

A dusting powder comprises a compound of the invention intimately mixed and ground with a solid pulverulent diluent, for example, kaolin.

A granular solid comprises a compound of the invention associated with similar diluents to those which may be employed in dusting powders, but the mixture is granulated by known methods. Alternatively it comprises the active ingredient absorbed or adsorbed on a pre-granular diluent, for example, Fuller's earth, attapulgite or limestone grit.

Wettable powders, granules or grains usually comprise the active ingredient in admixture with a suitable surfactant and an inert powder diluent such as china clay.

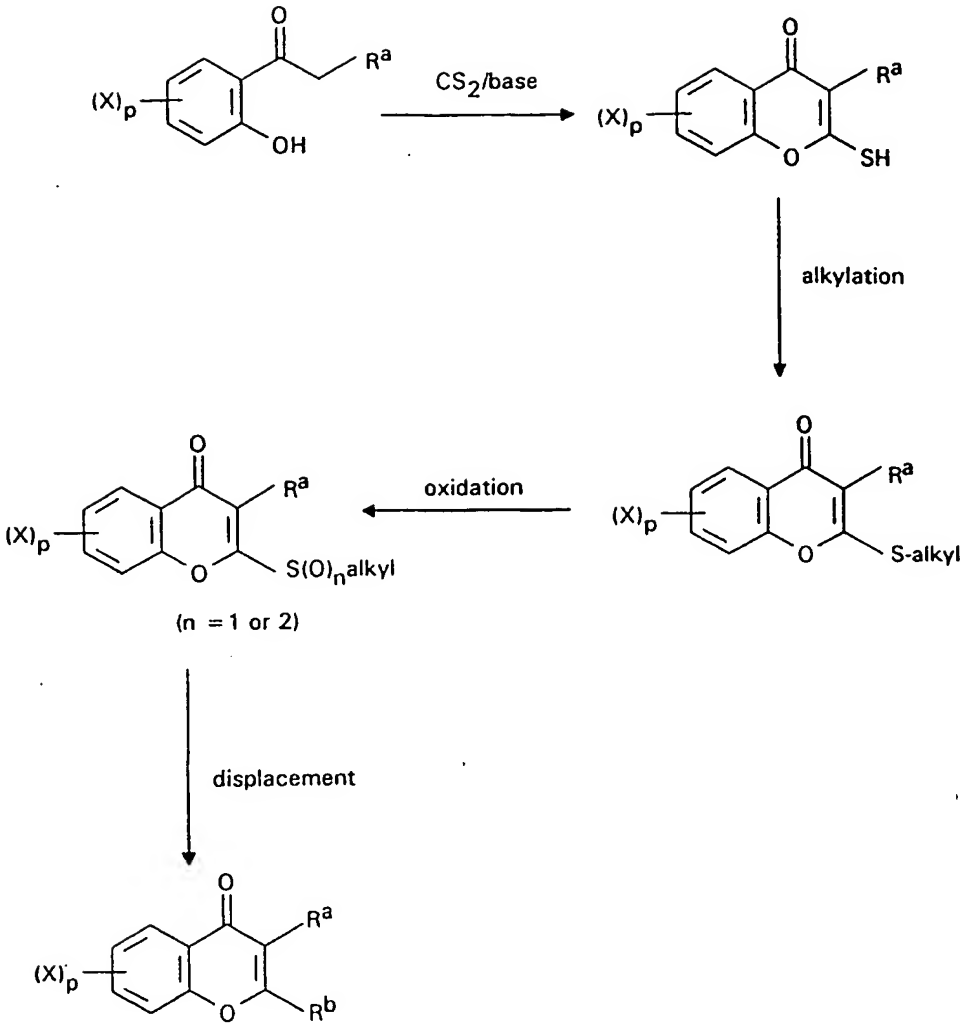
Another suitable concentrate is a flowable suspension concentrate which is formed by grinding the compound with water or other liquid, a wetting agent and a suspending agent.

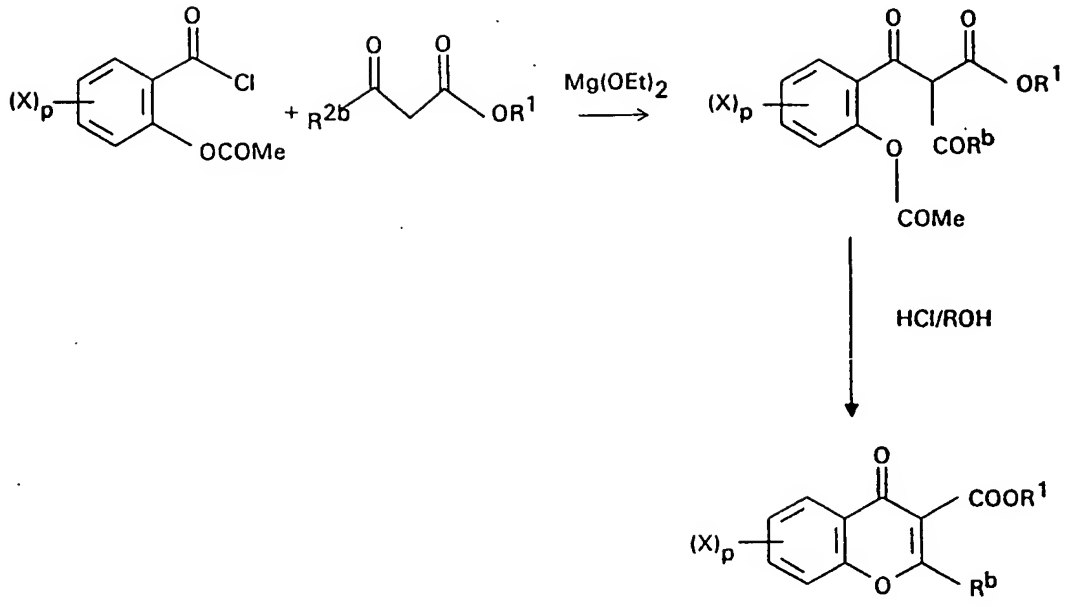
The concentration of the active ingredient in the composition of the present invention, as applied to plants is preferably within the range of 0.0001 to 1.0 per cent by weight, especially 0.0001 to 0.01 per cent by weight. In a primary composition, the amount of active ingredient can vary widely and can be, for example, from 5 to 95 per cent by weight of the composition.

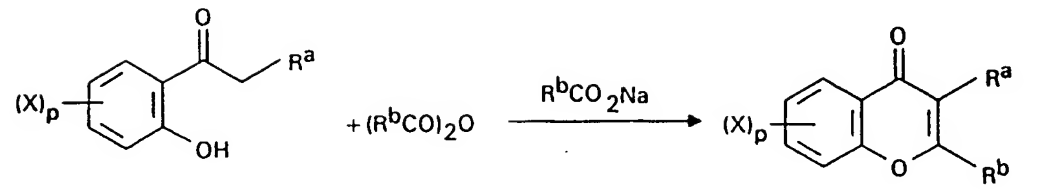
In the method of the invention the compound is generally applied to seeds, plants or their habitat. Thus, the compound can be applied directly to the soil before, at or after drilling so that the presence of active compound in the soil can control the growth of fungi which may attack seeds. When the soil is treated directly the active compound can be applied in any manner which allows it to be intimately mixed with the soil such as by spraying, by broadcasting a solid form of granules, or by applying the active ingredient at the same time as drilling by inserting it in the same drill as the seeds. A suitable application rate is within the range of from 5 to 1000 g per hectare, more preferably from 10 to 500 g per hectare.

Alternatively the active compound can be applied directly to the plant by, for example, spraying or dusting either at the time when the fungus has begun to appear on the plant or before the appearance of fungus as a protective measure. In both such cases the preferred mode of application is by foliar spraying. It is generally important to obtain good control of fungi in the early stages of plant growth as this is the time when the plant can be most severely damaged. The spray or dust can conveniently contain a pre- or post-emergence herbicide if this is thought necessary. Sometimes, it is practicable to treat the roots of a plant before or during planting, for example, by dipping the roots in a suitable liquid or solid composition. When the active compound is applied directly to the plant a suitable rate of application is from 0.025 to 5 kg per hectare, preferably from 0.05 to 1 kg per hectare.

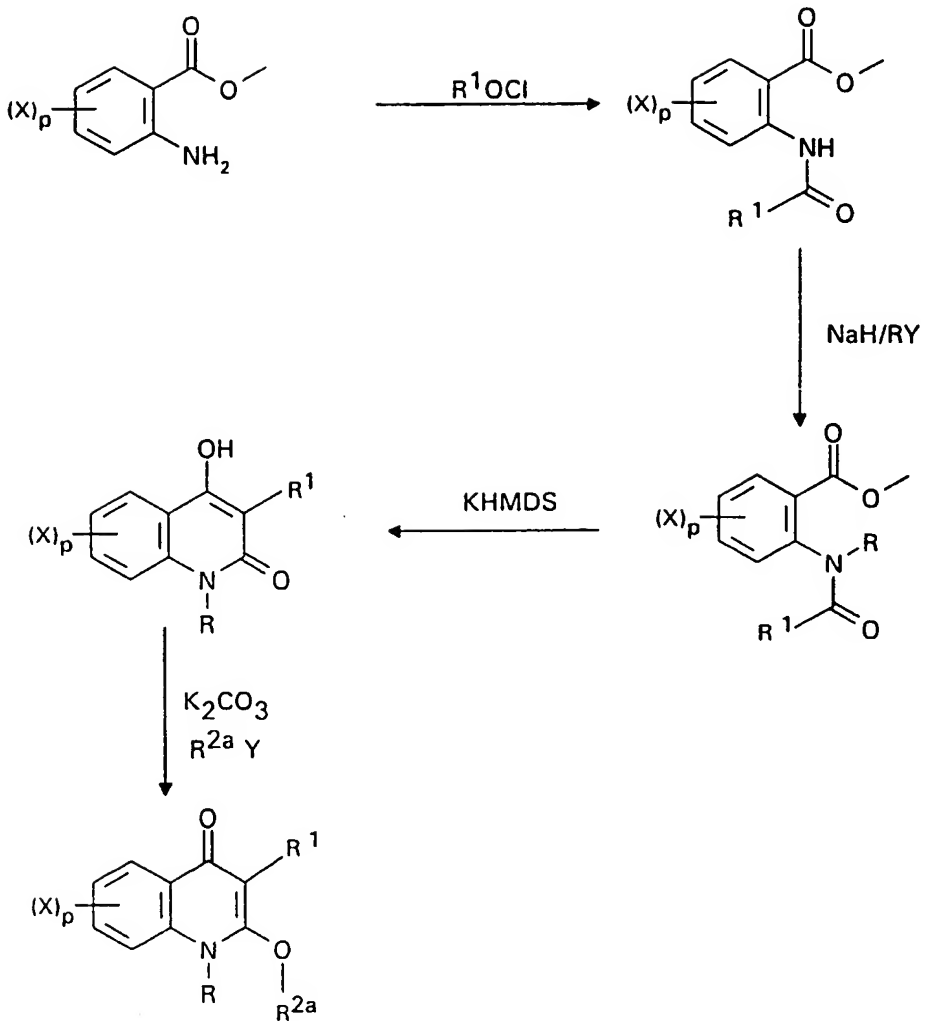
The novel compounds of the invention can be prepared in various ways in known manner. Typical methods are shown in the following reaction schemes


CS_2/base
alkylation
oxidation
displacement
(n = 1 or 2)

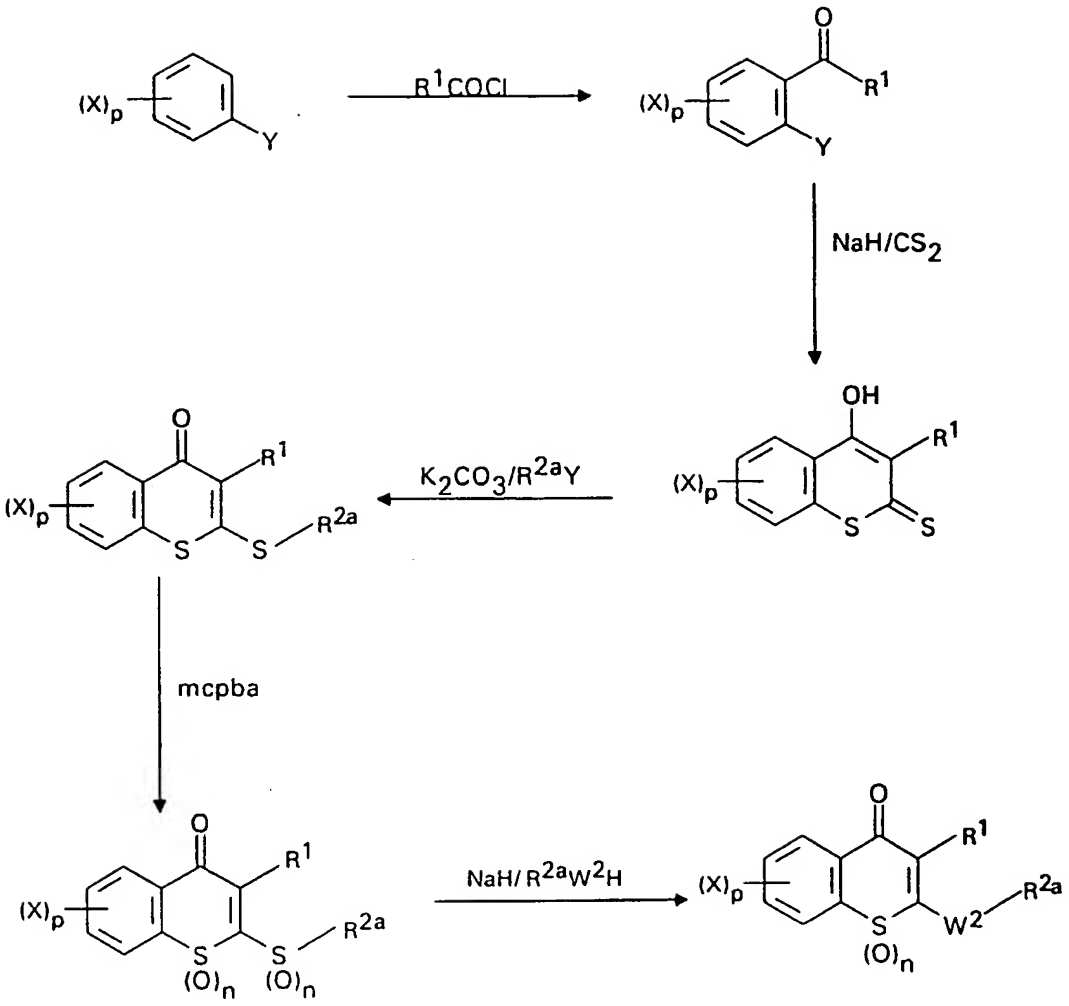

(X)p
Cl
OCOMe
+ R2b
OR1
Mg(OEt)2
(X)p
OR1
CORb
COMe
HCl/ROH
(X)p
COOR1
Rb

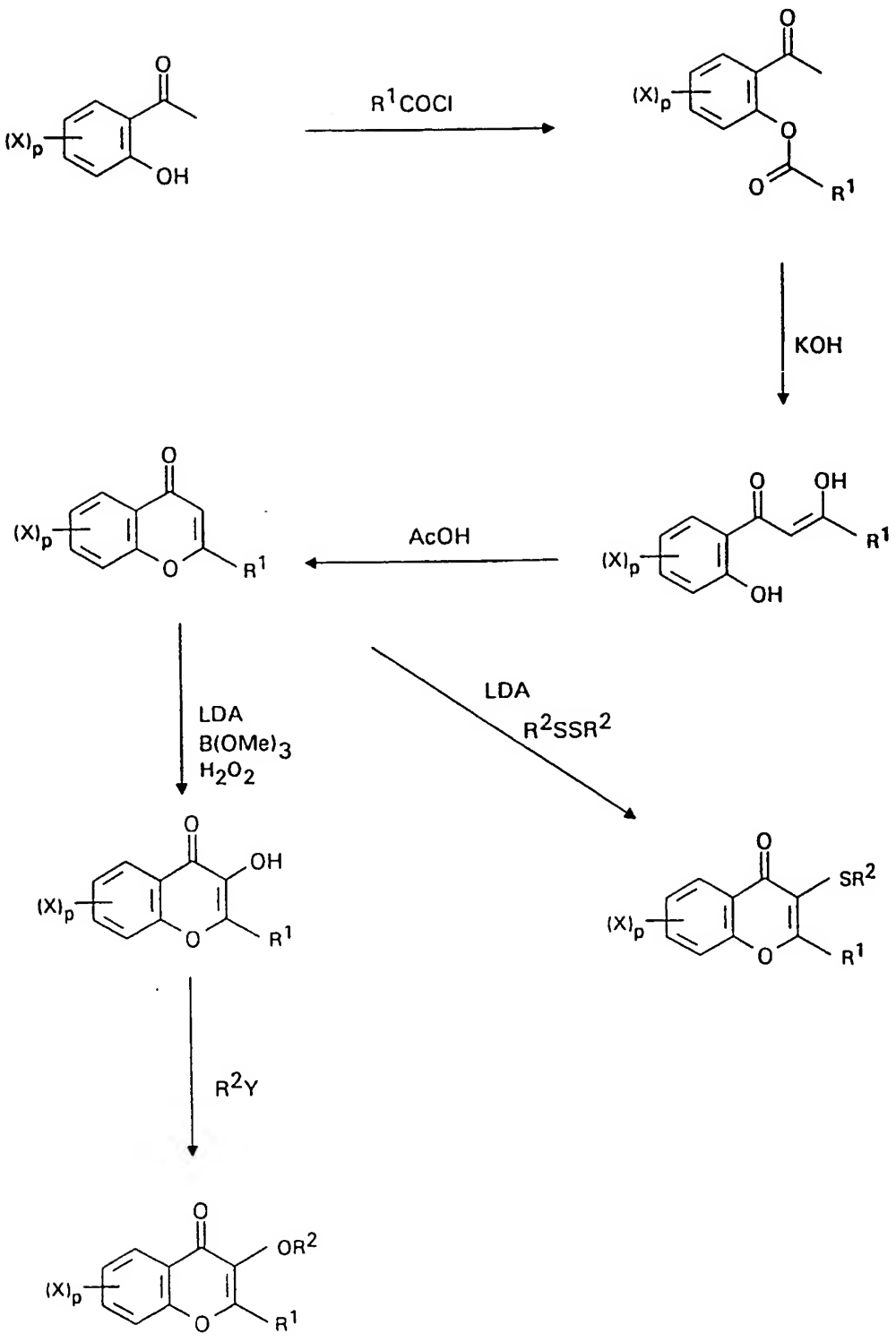

(X)p
Ra
OH
+ (RbCO)2O
RbCO2Na
(X)p
Ra
Rb

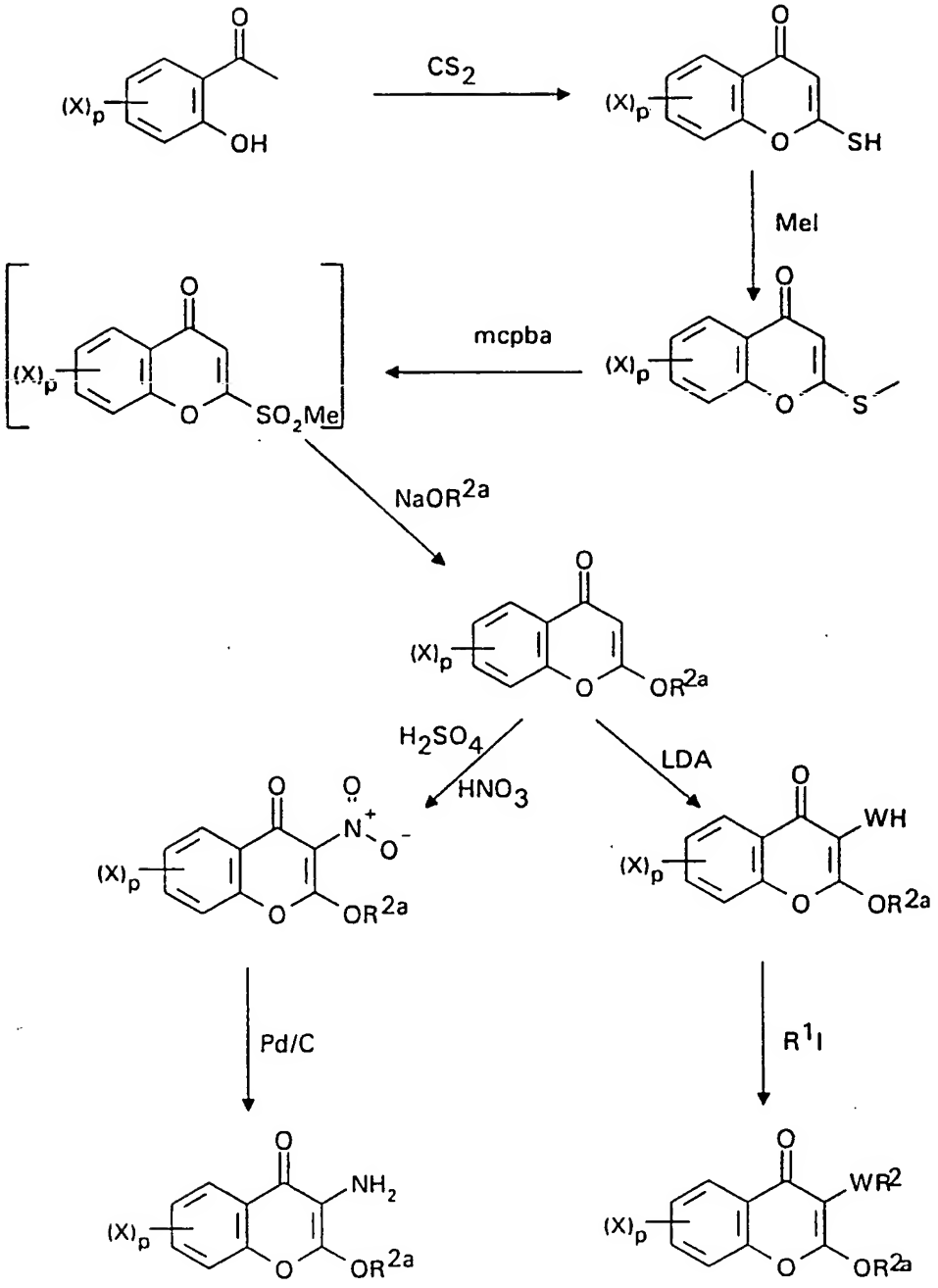
5



Y = leaving group, e.g. halogen or tosyl.


R1COCl
NaH/CS2
K2CO3/R2aY
mcpba
NaH/R2aW2H


R1COCl
KOH
AcOH
LDA
B(OMe)3
H2O2
LDA
R2SSR2
R2Y



The various R and X groups may be modified in known manner to give other desired values for these groups.

Other known methods may be used such as described for example in Tetrahedron 1979,35,551. Other methods will also be apparent to the chemist skilled in the art as will be the methods for preparing starting materials and intermediates. The Examples

also make apparent various methods of preparing compounds of the invention as well as starting materials and intermediates.

The invention is illustrated in the following Examples. Structures of isolated novel compounds were confirmed by NMR and/or other appropriate analyses.

Example 1

Pentanoyl chloride (19.4 ml) was added dropwise to 4-chlorophenol (20 g) in pyridine (100 ml) at 0°C. The reaction mixture was stirred at room temperature for 1 hour. The mixture was evaporated under reduced pressure, the residue extracted with diethyl ether and the extract washed with water, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, dried and evaporated to give 4-chlorophenyl pentanoate.

Aluminium trichloride (30.08 g) was added portionwise with stirring to this product (16.5 g) and the reaction mixture was heated at 165°C for 1 hour. The mixture was cooled and quenched with ice/hydrochloric acid (1N), extracted with diethyl ether and the extract washed with brine, dried over magnesium sulfate, filtered and evaporated to give 1-(5-chloro-2-hydroxyphenyl)-1-pentanone, as an oil.

A solution of this compound (21.2 g) in toluene (400 ml) was treated with carbon disulfide (6.2 ml) and then with potassium *tert*-butoxide (33.6 g), with stirring. The mixture was stirred at room temperature overnight. The mixture was acidified with acetic acid and then evaporated under reduced pressure. The residue was suspended in water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, filtered and evaporated. The residue was recrystallised from toluene to give 6-chloro-2-mercapto-3-propyl-4H-1-benzopyran-4-one, m.p. 143-5°C.

A solution of this compound (22.8 g) in dry acetone (300 ml) was stirred with potassium carbonate (7 g). After 10 minutes, methyl iodide (6.5 ml) was added. The mixture was stirred for 3 hours at room temperature and evaporated under reduced pressure. The residue was added to water and extracted with dichloromethane. The extract was dried over magnesium sulfate, filtered and evaporated and the residue

recrystallised from light petroleum (b.p. 80-100°C) to give 6-chloro-2-methylthio-3-propyl-4H-1-benzopyran-4-one, m.p. 107-10°C.

A solution of this compound (15.3 g) in dichloromethane (500 ml) was stirred overnight with *meta*-chloroperbenzoic acid (55 g of ca. 50%). The mixture was washed with aqueous sodium carbonate, aqueous ferrous sulfate and water, dried and evaporated. The residue was recrystallised from cyclohexane to give 6-chloro-2-methylsulfonyl-3-propyl-4H-1-benzopyran-4-one, m.p. 127-9°C.

Ethyl cyanoacetate (1.2 ml) was added to a stirred suspension of sodium hydride (0.44 g; 60% in oil) in dried tetrahydrofuran (100 ml). The mixture was stirred for 30 minutes and then the previous product (1 g) in dry tetrahydrofuran (25 ml) was added. The mixture was heated under reflux for 2 hours and then cooled and evaporated under reduced pressure. The residue was dissolved in water and acidified with acetic acid. The mixture was extracted with diethyl ether and the extract washed with water, dried over magnesium sulfate and evaporated under reduced pressure. The residue was re-crystallised from cyclohexane to give ethyl (6-chloro-4-oxo-3-propyl-4H-1-benzopyran-2-yl)(cyano)acetate, m.p. 115-7°C. (Compound 1)

SN 632499

Example 2

A solution of 5'-bromo-2'-hydroxyacetophenone (16.94 g) in toluene (140 ml) was added to a cooled mixture of sodium methoxide (13.8 g) in a solution of ethyl formate (31.5 ml) in toluene (100 ml). The mixture was stirred for 2 hours and allowed to stand overnight at room temperature. Water (250 ml) was added and the mixture filtered. The aqueous layer was separated and neutralised with acetic acid. The solid precipitate was filtered to give (5-bromo-2-hydroxybenzoyl)acetaldehyde.

A solution of this compound (14.2 g) in dimethyl sulfoxide (116 ml) was cooled in ice-water. Aqueous potassium hydroxide (7 g in 23 ml water) was added, followed by carbon disulfide (11.1 ml). The mixture was stirred at about 10°C for 4 hours. Methyl iodide (14.2 ml) was added dropwise with cooling. The mixture was stirred for 2 hours at room temperature, poured into ice-water and filtered. The precipitate was washed with water, dried and triturated with diethyl ether. The solid that remained was heated with methyl ethyl ketone (100 ml) and filtered hot. The solid was purified by silica gel

column chromatography to give 6-bromo-2-methylthio-4-oxo-4H-1-benzopyran-3-carbaldehyde, m.p. 155-6°C.

This compound (6.9 g) was added to a solution of sodium hydride (2.8 g; 60% dispersion in oil) in butanol (150 ml). The mixture was stirred for 45 minutes, acidified with acetic acid and extracted with dichloromethane. The extract was washed with aqueous sodium hydrogen carbonate, dried and evaporated. The residue was purified by silica gel column chromatography to give butyl 6-bromo-4-oxo-4H-1-benzopyran-3-carboxylate, m.p. 95-6°C.

Butyl lithium (3.6 ml; 2.5M in hexane) was added to a suspension of copper bromide dimethyl sulfide (0.92 g) in dry diethyl ether at -20°C and the mixture cooled to -40°C. A solution of the previous reaction product (0.97 g) in dry diethyl ether (50 ml) was the added dropwise to this solution. The mixture was stirred at this temperature for 30 minutes and the quenched with aqueous saturated ammonium chloride. The mixture was allowed to warm to room temperature, filtered and the filtrate washed with brine, dried and evaporated. The residue was purified by silica gel column chromatography to give a product which was taken up in diethyl ether, washed with dilute hydrochloric acid, dried and evaporated to give butyl 6-bromo-2-butyl-2,3-dihydro-4-oxo-4H-1-benzopyran-3-carboxylate, as a colourless oil.

A mixture of this compound (4.38 g) and 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (2.85 g) in dioxane (25 ml) was heated at 40°C for 7 hours. The mixture was allowed to stand at room temperature overnight, filtered and the solid washed with ethyl acetate. The combined organic solution was washed with aqueous sodium carbonate, brine, dried and evaporated. The residue was stirred with diisopropyl ether and filtered and the solution evaporated. The residue was purified by silica gel column chromatography to give butyl 6-bromo-2-butyl-4-oxo-4H-1-benzopyran-3-carboxylate, as an oil. (Compound 2)

Example 3

In a similar manner to that described in Example 1, there was obtained 6-bromo-3-butyl-2-methylsulfonyl-4H-1-benzopyran-4-one, m.p. 130-1°C.

A solution of this compound (72 mg) in acetonitrile (1.4 ml) and ethanol (0.4 ml) with potassium cyanide (16 mg) was stirred at room temperature overnight. The mixture was extracted with ethyl acetate and the extract dried and evaporated under reduced pressure to give 6-bromo-3-butyl-2-cyano-4H-1-benzopyran-4-one, m.p. 76-9°C. (Compound 3)

Example 4

A mixture of methyl acetoacetate (3.2 ml) and magnesium ethoxide (3.42 g) in dry toluene (30 ml) was heated under reflux for 2 hours. The mixture was cooled to 0°C and a solution of 5-bromo-2-acetoxybenzoyl chloride was added dropwise and the mixture stirred overnight at room temperature. It was evaporated under reduced pressure and the residue heated to reflux with ethanol (40 ml) and acetyl chloride (0.7 ml). It was then cooled and evaporated under reduced pressure. The residue was extracted with dichloromethane and the extract washed with aqueous sodium hydrogen carbonate, dried and evaporated under reduced pressure. The residue was triturated with light petroleum (b.p. 40-60°C), filtered and the residue purified by silica gel chromatography to give methyl 6-bromo-2-methyl-4-oxo-4H-1-benzopyran-3-carboxylate, m.p. 122-4°C (compound 4a) and ethyl 6-bromo-2-methyl-4-oxo-4H-1-benzopyran-3-carboxylate, m.p. 87-9°C (compound 4b).

Example 5

A mixture of butyric anhydride (6.2 g), sodium butyrate (3.9 g) and 1-(5-methyl-2-hydroxyphenyl)-1-pentanone (3 g) in dichlorobenzene (9.6 g), was heated under reflux for 6 hours. The mixture was poured into water and extracted with diethyl ether. The extract was washed with aqueous sodium carbonate, brine, dried and evaporated. The residue was purified by silica gel column chromatography to give 6-methyl-2,3-dipropyl-4H-1-benzopyran-4-one as a yellow oil. (compound 5)

Example 6

Sodium hydride (0.53 g of 60% solution in oil) was added portionwise over 2 hours to a solution of 2',4'-dichloropropiophenone (2.03 g) and carbon disulfide (1.3 ml) in dry dimethylformamide (12 ml) and dry toluene (40 ml) at 5°C. The mixture was stirred at room temperature for one hour. Excess sodium hydride was quenched with 2-propanol and the mixture heated at 110°C for 1½ hours. It was cooled, added to water (30 ml) and acetic acid (0.5 ml) added. The mixture was extracted with diethyl

ether and the extract washed with water. The combined aqueous phases were acidified with hydrochloric acid, and the precipitate filtered and dried to give crude 7-chloro-4-hydroxy-3-methyl-2*H*-1-benzothiopyran-2-thione.

Methyl iodide (0.31 ml) was added to a solution of this compound (1.1 g) and potassium carbonate (0.69 g) in dry acetone (10 ml). The mixture was stirred for a short time at room temperature and the solvent evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate and the aqueous layer extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine and dried over magnesium sulfate and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate to give 7-chloro-3-methyl-2-methylthio-4*H*-1-benzothiopyran-4-one, m.p. 156-7°C (Compound 6)

Example 7

Valeryl chloride (10.55 ml) was added dropwise over 45 minutes to 1,4-dibromobenzene (20 g) and anhydrous aluminium chloride (15.8 g) at a temperature of 80°C. The mixture was heated at 110°C for 5 hours and then left to stand overnight. The mixture was poured into ice water (100 ml) and extracted with ethyl acetate. The extracts were washed with water and dilute brine, dried over magnesium sulfate, and evaporated under reduced pressure to give crude 2',5'-dibromopentanophenone.

In a similar manner to Example 6 this was reacted with sodium hydride and carbon disulfide to give 6-bromo-4-hydroxy-3-propyl-2*H*-1-benzothiopyran-2-thione, which in turn was reacted with methyl iodide to give 6-bromo-2-methylthio-3-propyl-4*H*-1-benzothiopyran-4-one, m.p. 82-3 °C (Compound 7)

Example 8

Sodium hydride (0.1 g of 60% solution in oil) was added to phenol (0.41 g) in dry tetrahydrofuran (15 ml). The mixture was stirred at room temperature for 15 minutes. Compound 2 (1 g) was added, followed by dimethylformamide (15 ml) and tetrahydrofuran (15 ml). The mixture was heated under reflux for 12 hours, cooled and poured into water. The mixture was extracted with ether and the extract washed with water, brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to

give 2-methylthio-6-phenoxy-3-propyl-4*H*-1-benzothiopyran-4-one, as a yellow oil (Compound 8).

In a similar manner, using butanol instead of phenol there was obtained, 6-butoxy-2-methylthio-3-propyl-4*H*-1-benzothiopyran-4-one, m.p. 62-3 °C, (Compound 8a).

Example 9

meta-Chloroperbenzoic acid, (2.49 g of 50%) was dissolved in dichloromethane (25 ml) which had been dried with magnesium sulfate. The mixture was filtered and the solution added dropwise to compound 2 (1.4 g) in dry dichloromethane (15 ml). The mixture was stirred at room temperature overnight, washed with saturated aqueous sodium hydrogen carbonate, aqueous sodium sulfite (10%) and brine. The mixture was dried, filtered and evaporated and the residue purified by silica gel column chromatography to give 6-bromo-2-methylsulfonyl-3-propyl-4*H*-1-benzothiopyran-4-one, 175-9 °C (Compound 9), and
6-bromo-2-methylsulfinyl-3-propyl-4*H*-1-benzothiopyran-4-one, 136-7 °C (Compound 9a).

Example 10

In a similar manner to that described in Example 8, compound 9 was reacted with butanol to give 6-bromo-2-butoxy-3-propyl-4*H*-1-benzothiopyran-4-one, m.p. 78-80°C. (Compound 10)

Example 11

In a similar manner to Example 6, 2',4',-dichloropropiophenone was reacted with phenyl isothiocyanate followed by methyl iodide to give 7-chloro-3-methyl-2-methylthio-1-phenyl-4-quinolone, m.p. 200-2 °C.(Compound 11).

In a similar manner to Example 9 this was converted to crude 7-chloro-3-methyl-2-methylsulfonyl-1-phenyl-4-quinolone, which, in a similar manner to Example 10, was converted to crude 2-butoxy-7-chloro-3-methyl-1-phenyl-4-quinolone, m.p. 131-2 °C.(Compound 11a)

Example 12

Valeryl chloride (8.7 ml) was added, dropwise, to a solution of methyl 5-bromoanthranilate (13.6 g) and triethylamine (10.3 ml) in dry dichloromethane (100 ml) at room temperature over 10 minutes. The mixture was filtered and the filtrate washed with 1M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and saturated brine and dried and evaporated under reduced pressure. The residue was allowed to stand and a solid recrystallised from a mixture of diisopropyl ether and cyclohexane to give methyl 5-bromo-N-valerylanthranilate, m.p. 53.5-5°C.

A solution of this compound (6 g) in tetrahydrofuran (100 ml) was treated with sodium hydride (0.92 g of 60% oil dispersion) and the mixture stirred at room temperature for 30 minutes. Methyl iodide (1.3 ml) was added and the mixture allowed to stand overnight. Saturated aqueous ammonium chloride (10 ml) was added and the tetrahydrofuran evaporated under reduced pressure. The residue was extracted with ethyl acetate and the extracts washed with saturated aqueous sodium hydrogen carbonate and saturated brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give methyl 5-bromo-N-methyl-N-valerylanthranilate, as an oil.

To this product (4 g) suspended in dry tetrahydrofuran (25 ml) was added, dropwise, potassium hexamethyldisilazide (32 ml of 5M toluene solution) at -78°C. The mixture was allowed to warm to room temperature and trifluoroacetic acid (2.5 ml) was added. The mixture was filtered and the solid washed with ether. The filtrate was evaporated under reduced pressure and the residue extracted with ethyl acetate, the extract washed with water, saturated brine and dried over magnesium sulfate and evaporated under reduced pressure. The residue was redissolved in ethyl acetate/ dichloromethane and the solution worked up to give 6-bromo-4-hydroxy-1-methyl-3-propyl-2-quinolone, as pale yellow .

A mixture of a solution of this product (1 g) in dimethylformamide (5 ml) and potassium carbonate (0.56 g) was stirred for 5 minutes under nitrogen. 1-Bromobutane (0.44 ml) was added dropwise and the mixture heated at 80°C for 21 hours and then allowed to cool over the weekend. The mixture was worked up in conventional manner including final purification by silica gel column chromatography

to give 6-bromo-2-butoxy-1-methyl-3-propyl-4-quinolone, as an off-white solid. (Compound 12)

Example 13

Triethylamine (2.82 g) was added to solution of 2-acetyl-4-bromophenol (5 g). The mixture was cooled to 0 °C and 4-chlorobenzoyl chloride (4.07 g). added. The mixture was left at room temperature overnight under a nitrogen atmosphere. The mixture was quenched with water and the organic layer washed with 2N hydrochloric acid, aqueous sodium hydrogen carbonate, 2N hydrochloric acid and dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with light petroleum (b.p. 40-60 °C) to give 2-acetyl-4-bromophenyl 4-chlorobenzoate, as an off white solid.

Potassium hydroxide pellets (1.2 g) was added to a solution of this compound (5.g) in dry pyridine (50 ml) maintained at 50 °C, The mixture was stirred at this temperature until all the starting material was consumed (determined by tlc). The mixture was cooled to room temperature and added to acetic acid (300 ml; 20%). the precipitate was filtered, washed with water, dried and dissolved in dichloromethane. The solution was dried over magnesium sulfate and evaporated under reduced pressure to give 1-(5-bromo-2-hydroxyphenyl)-3-(4-chlorophenyl)-3-hydroxyprop-2-en-1-one, as a pale yellow solid.

A suspension of this compound (3 g) in glacial acetic acid (50 ml) was heated at 100-10 °C until all the starting material was consumed (determined by tlc). The mixture was cooled to room temperature, diluted with ethyl acetate, neutralised with sodium hydroxide/sodium hydrogen carbonate and added to acetic acid (300 ml; 20%). The aqueous layer was extracted with ethyl acetate and the combined ethyl acetate layers dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with light petroleum (b.p. 40-60 °C) to give 6-bromo-2-(4-chlorophenyl)-4*H*-1-benzopyran-4-one, as off white solid

Butyllithium (2.5 molar in hexane; 2.4 ml), was added to tetrahydrofuran (50 ml) at -70-80°C, followed by diisopropylamine (0.84 ml). The mixture was stirred at this temperature for 30 minutes. The previous product compound (1 g) was added and the mixture stirred for 30 minutes at -70 °C. Trimethyl borate (0.34 ml) was added and the

mixture stirred at -78°C for 35 minutes. The mixture was then treated with acetic acid (0.27 g) and hydrogen peroxide (0.84 ml of 30%). The mixture was then allowed to warm to room temperature and stirred overnight under nitrogen.

The mixture was quenched with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give crude 6-bromo-2-(4-chlorophenyl)-3-hydroxy-4*H*-1-benzopyran-4-one.

A solution of this compound (54.6 mg) in dry dimethylformamide under nitrogen was treated with potassium carbonate (0.02 g). 1-Bromopropane (0.019 g) was added and the mixture stirred at 50°C for one hour. The mixture was cooled to room temperature, evaporated under reduced pressure and the residue taken up in ethyl acetate and partitioned between water and ethyl acetate. The aqueous layer was further extracted with ethyl acetate and the combined extracts washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 6-bromo-3-propoxy-2-(4-chlorophenyl)-4*H*-1-benzopyran-4-one, m.p. 120-2 °C (Compound 13).

In a similar manner using dimethyl disulphide instead of trimethyl borate/hydrogen peroxide there was obtained 6-bromo-3-methylthio-2-(4-chlorophenyl)-4*H*-1-benzopyran-4-one, m.p. 134-6 °C (Compound 14), and 6-bromo-3,5-dimethylthio-2-(4-chlorophenyl)-4*H*-1-benzopyran-4-one, m.p. 141-3 °C (Compound 15).

Example 16

A solution of 2-acetyl-4-bromophenol (20 g) and carbon disulfide (7 ml) in toluene (400 ml) was added dropwise to a suspension of potassium tert-butoxide (31.4 g) in toluene (500 ml) at 10°C. The mixture was stirred at room temperature for 72 hours. Glacial acetic acid (35 ml) was added and the mixture evaporated under reduced pressure. The residue was treated with water (200 ml) and glacial acetic acid (20 ml) to precipitate an oily solid. Light petroleum (b.p. 40-60°C) was added and the mixture

stirred for one hour, filtered and the solid was collected and washed with light petroleum to give 6-bromo-2-mercapto-4*H*-1-benzopyran-4-one, m.p. 230 °C.

A solution of this compound 1 (5.4 g) in acetone (150 ml) was stirred with potassium carbonate (3.1 g) and methyl iodide (3 ml) added. The mixture was stirred for 1 hour, filtered and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with water, dried, filtered and evaporated under reduced pressure and the residue purified by silica gel chromatography to give 6-bromo-2-methylthio-4*H*-1-benzopyran-4-one, as pale yellow solid.

A solution of *meta*-chloroperbenzoic acid (18.65g of 50% pure material) in dichloromethane (100 ml) was added to a solution of this compound (4.83 g) in dichloromethane (40 ml) and the mixture stirred overnight at room temperature.

This solution (now comprising 6-bromo-2-methylsulfonyl-4*H*-1-benzopyran-4-one) was added to a solution of sodium methoxide (7.35 g) in methanol (130 ml) and the mixture stirred at room temperature for 1 hour and then evaporated under reduced pressure. Water (50 ml) was added and the mixture extracted with dichloromethane. The extract was dried and evaporated under reduced pressure, to give crude 6-bromo-2-methoxy-4*H*-1-benzopyran-4-one.

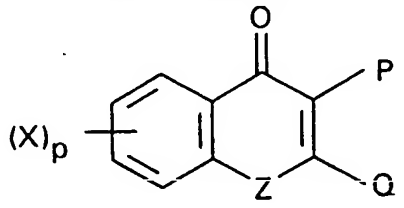
This compound (1.2.g) was added portionwise to cold concentrated sulfuric acid (4.8 ml). A mixture of concentrated nitric acid (0.38 ml) with concentrated sulfuric acid (1.4 ml) was added dropwise with cooling and the mixture stirred at 5 °C for 45 minutes and at room temperature for 30 minutes. The mixture was added to ice and ethyl acetate (500 ml) added. The mixture was neutralised with solid sodium hydrogen carbonate, filtered and the organic layer dried and evaporated under reduced pressure to give 6-bromo-2-methoxy-3-nitro-4*H*-1-benzopyran-4-one, m.p. 189-91°C (compound 16)

Example 17

A suspension of compound 1 (0.88 g) in methanol (50 ml) was hydrogenated using palladium charcoal as catalyst, until no further uptake of hydrogen occurred. The reaction mixture was filtered, dried and evaporated under reduced pressure. The

residue was triturated with diethyl ether to give 3-amino-6-bromo-2-methoxy-4*H*-1-benzopyran-4-one, m.p. 226-8°C (dec.) (compound 17)

The following compounds of the invention and intermediates were prepared in an analogous manner to one of the previous examples.



Cpd	P	Q	Z	$(X)_p$	m.p. (°C)
18	Pr	Pr	O	6-Br	72
19	Pr	-C(COOEt)$_2$Bu	O	6-Br	oil
20	COOMe	3-butenyl	O	6-Br	57-8
21	COOEt	3-butenyl	O	6-Br	59-60
22	COOEt	Pr	O	6-Br	64-5
23	COOPr^i	Pr	O	6-Br	51-3
24	Ph	O-pentyl	N-Me	-	oil
25	2,4-Cl$_2$Ph	1,2,4-triazol-1-yl	NH	-	oil
26	Me	O-Bu	N-Ph	7-Cl	131-2
27	Pr	O-Bu	S	6-Br	78-80
28	Pr	O-(CH$_2$)$_2$OMe	S	6-SMe	52-4
29	Me	SO$_2$Me	S	7-Cl	226-7
30	Pr	SO$_2$Me	S=O	6-Br	138-9
31	Pr	SOMe	S=O	6-Br	140-1
32	Pr	S-Me	S	6-SMe	121-3
33	O-SO$_2$ -(2-CF$_3$-Ph)	Ph	O	-	162-3
34	imidazol-1-yl	2,4-Cl$_2$Ph	O	-	198-200
35	1,2,4-triazol-1-yl	2,4-Cl$_2$Ph	O	-	226-8

Test Example

Compounds are assessed for activity against one or more of the following:

Plasmopara viticola: vine downy mildew

Erysiphe graminis: *f sp. hordei*; barley powdery mildew

Erysiphe graminis f. sp. tritici, wheat powdery mildew

Pyricularia oryzae: rice blast

Botrytis cinerea: grey mould

Leptosphaeria nodorum: glume blotch

Venturia inaequalis: apple scab

Aqueous solutions or dispersions of the compounds at the desired concentration, including a wetting agent, were applied by spray or by drenching the stem base of the test plants, as appropriate. Plants or plant parts were then inoculated with appropriate test pathogens and kept under controlled environment conditions suitable for maintaining plant growth and development of the disease. After an appropriate time, the degree of infection of the affected part of the plant was visually estimated. Compounds are assessed on a score of 1 to 3 where 1 is little or no control, 2 is moderate control and 3 is good to total control. At a concentration of 500 ppm (w/v) or less, the following compounds scored 2 or more against the fungi specified

Plasmopara viticola

4b, 5, 8, 18, 33, 34.

Erysiphe graminis: f sp. hordei

34,25

Erysiphe graminis f. sp. tritici

1-7, 8a, 9, 12-14, 16, 18, 20, 21, 29, 32, 34, 35

Pyricularia oryzae

4b, 26

Botrytis cinerea

7, 29, 31

Leptosphaeria nodorum

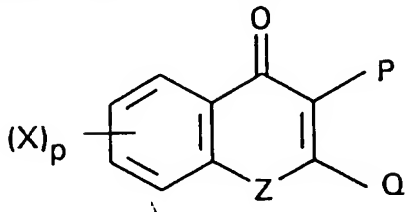
7, 19

Venturia inaequalis

33

CLAIMS

1. The use as fungicides of compounds of formula I



(I)

in which

Z is O, $S(O)_n$ or NR, and

a) P is WR^2; and Q is R^1 or W^2R^{2a} or

b) P is R^a and Q is R^b;

and when Z is $S(O)_n$ or NR, and Q is W^2R^{2a}; P can be R^1;

W and W^2, which may be the same or different, are O, $S(O)_n$, $N(R^3)$, $N(R^3)N(R^4)$, $N(R^3)O$ or $ON(R^3)$;

R^1 is hydrogen, or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, phenyl or heterocyclyl group;

R, R^2, R^{2a}, R^{2b}, R^3 and R^4, which may be the same or different, have the same meaning as R^1, or are acyl, or

any two adjacent R groups together with the atoms to which they are attached form an optionally substituted ring which may contain other hetero atoms;

R^a and R^b, which may be the same or different, have the same meaning as R^1 (heterocyclyl groups being carbon linked) or are cyano, nitro, $COOR^1$ or COR^1,

each X, which may be the same as or different from any other X, is halogen, CN, NO_2, SF_5, $B(OH)_2$, trialkylsilyl or a group E, OE or SE where E is a group as defined hereinbefore for R^a or is optionally substituted amino; or two adjacent groups X together with the atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

n is 0, 1 or 2; and

p is 0 to 4.

with the proviso that P and Q are not both hydrogen.

2) Novel compounds of formula I as defined in claim 1.

3). A fungicidal composition which comprises a compound of formula I as defined in claim 1 in admixture with an agriculturally acceptable diluent or carrier.

5

4). A method of combating phytopathogenic fungi, at a locus infested or liable to be infested therewith, which comprises applying to the locus a compound of formula I as defined in claim 1.

4047633
4047635

CHROMONES USEFUL AS FUNGICIDES

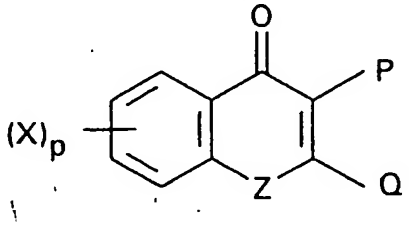
Field of the invention

This invention relates to chromones useful as fungicides.

Description of the invention

We have now found that certain chromones have particularly valuable fungicidal properties

In one aspect, the invention provides the use as fungicides of compounds of formula I



(I)

in which

Z is O, $S(O)_n$ or NR, and

a) P is WR^2; and Q is R^1 or W^2R^{2a} or

b) P is R^a and Q is R^b;

and when Z is $S(O)_n$ or NR, and Q is W^2R^{2a}; P can be R^1;

W and W^2, which may be the same or different, are O, $S(O)_n$, $N(R^3)$, $N(R^3)N(R^4)$, $N(R^3)O$ or $ON(R^3)$;

R^1 is hydrogen, or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, phenyl or heterocyclyl group;

R, R^2, R^{2a}, R^{2b}, R^3 and R^4, which may be the same or different, have the same meaning as R^1, or are acyl, or

any two adjacent R groups together with the atoms to which they are attached form an optionally substituted ring which may contain other hetero atoms;

R^a and R^b, which may be the same or different, have the same meaning as R^1 (heterocyclyl groups being carbon linked) or are cyano, nitro, $COOR^1$ or COR^1,

each X, which may be the same as or different from any other X, is halogen, CN, NO_2, SF_5, $B(OH)_2$, trialkylsilyl or a group E, OE or SE where E is a group as